Docket No.
251305/0028
SBP:AEW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: **David Zhang, et al.** Group Art Unit: **1634**

Application No.: **09/978,261** Examiner: **Frank Lu**

Filed: **October 15, 2001**

For: **NUCLEIC ACID AMPLIFICATION METHODS**

Date: January 25, 2007

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF AMY WILSON

I, AMY WILSON, hereby declare that:

1. I am a citizen of the United States, a registered patent agent at the law firm of Stroock & Stroock & Lavan LLP, having offices at 180 Maiden Lane, New York, NY 10038.

2. I make this Declaration to provide facts in support of a Petition for an Unintentionally Delayed Claim Under 37 C.F.R. § 1.78(a)(3).

3. This Declaration is being made based on my first-hand knowledge of the facts recited herein.

4. The United States Patent and Trademark Office issued an Office Action on July 28, 2006 in connection with U.S. Application Serial No. 09/978,261 (the "'261 Application"). The July 28, 2006 Office Action alleged that certain claims of the '261 Application were

unpatentable over Zhang, et al. (U.S. Patent No. 5,942,391) (the "Zhang Patent"). A true copy of the July 28, 2006 Office Action is annexed as Wilson Dec. Ex. A.

5. On January 19, 2007, in preparing a response to the July 28, 2006 Office Action I attempted to understand how the Zhang Patent, to which I believed the '261 Application claimed priority benefit, could be cited against the '261 Application, I reviewed the entire file history of the '261 Application.

6. During the file history review I discovered that when the '261 Application was originally filed on October 15, 2001, the claim for priority was inadvertently omitted.

7. Until the file history review in January of 2007 I was unaware that the claim for priority had not been included in the '261 Application.

8. I also discovered that, unaware of the priority claim oversight, another Applicants' Representative filed a Supplemental Declaration and Power of Attorney on November 6, 2002, which claimed priority to the prior-filed applications listed on the Amendment to the Specification on page 2 of this paper. A true copy of the Supplemental Declaration and Power of Attorney is annexed as Wilson Dec. Ex. B.

9. Once the oversight was discovered on January 19, 2007, I promptly prepared this Petition to correct the priority claim for the '261 Application.

10. I hereby declare that all statements made herein of my own knowledge are true; and all statements mad e on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code,

and that willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement was directed.

Dated: January 25, 2007

Amy Wilson

WILSON DECLARATION

EXHIBIT A

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,261	10/15/2001	David Y. Zhang	251305.0028 SBP/MCD	4119

7590 07/28/2006

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/978,261	Applicant(s) ZHANG, DAVID Y.
	Examiner Frank W [illegible]	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/6/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *4/5/2006*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on May 5, 2006 has been entered. The claims pending in this application are claims 40-52. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on May 5, 2006.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 40-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 40 and 47 recite the limitation "the signal" in (iii) of step (b). There is insufficient antecedent basis for this limitation in the claims because step (a), (i) and (ii) of the claims only mention a signal generating moiety and do not mention a signal. Please clarify.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 47, 48, 51, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang *et al.*, (US Patent NO. 5,567,583, published on October 22, 1996) in view of Harris (US Patent No. 5,837,469, published on November 17, 1998).

Regarding claim 47, since Wang *et al.*, teach a method for detecting a target nucleic acid, which method comprises the steps of: amplifying the target nucleic acid to obtain an amplification product using a polymerase, a first primer with or without a segment noncontiguous to a first priming sequence, and a second primer with or without a segment noncontiguous to a second priming sequence in the presence of an oligonucleotide which is incapable of acting as a primer for said polymerase, wherein said oligonucleotide has at least 5 consecutive nucleotides fully complementary to at least 5 consecutive nucleotides of said first primer; and detecting the presence of the target nucleic acid by monitoring the amplification thereof wherein a first fluorophore is covalently attached to said first primer and a second fluorophore is covalently attached to said oligonucleotide, with one of said first and second fluorophores being a donor fluorophore and the other being an acceptor fluorophore, so that when said first primer and said oligonucleotide are hybridized, said donor fluorophore and said acceptor fluorophore are in close proximity to allow resonance energy transfer therebetween; and, further, said detecting step is performed by monitoring fluorescent emission change of said acceptor fluorophore upon irradiation of said donor fluorophore with an excitation light, said change being a function of the extent of said first primer being dissociated from said oligonucleotide and being incorporated into said amplification product of the target nucleic acid (see columns 19 and 20, claims 1 and 3, column 3, second paragraph, and Figure 1), Wang *et al.*, disclose contacting the nucleic acid with an oligonucleotide primer pair comprising a first

~~primer (ie., the first primer taught by Wang *et al.,*) and a second primer (ie., the oligonucleotide~~ taught by Wang *et al.,*) under conditions that allow hybridization between complementary sequences in the target nucleic acid and the oligonucleotide primer pair wherein (i) the first primer of the pair comprises (A) a first sequence that is complementary to the target nucleic acid (ie., the first priming sequence taught by Wang *et al.,*), (B) a second sequence that is complementary to the second primer of the pair (ie., at least 5 consecutive nucleotides of said first primer taught by Wang *et al.,*), and (C) a signal generating moiety (ie., the first fluorophore or the donor fluorophore taught by Wang *et al.,*); (ii) the second primer of the pair (ie., the oligonucleotide taught by Wang *et al.,*) comprises (A) a sequence that is complementary to the first primer (ie., at least 5 consecutive nucleotides fully complementary to at least 5 consecutive nucleotides of said first primer taught by Wang *et al.,*); and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety (ie., the second fluorophore or the acceptor fluorophore taught by Wang *et al.,*); and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited (ie., the signal of the first fluorophore or the donor fluorophore is inhibited by the second fluorophore or the acceptor fluorophore due to fluorescence energy transfer); adding a single stranded oligonucleotide primer comprising sequences complementary to the target nucleic acid (ie., the second primer taught by Wang *et al.,*); adding a DNA polymerase; and amplifying the target nucleic acid and separating the signal generating moiety (ie., the donor fluorophore taught by Wang *et al.,*) and the quenching, masking or inhibitory moiety (ie., an acceptor fluorophore taught by Wang *et al.,*); thereby generating a signal as recited in claim 47.

Regarding claim 48, Wang *et al.*, teach that the signal generating moiety (ie., the first fluorophore on the first primer taught by taught by Wang *et al.*,) is a fluorescent agent (see columns 19 and 20, claims 1 and 3).

Regarding claims 51 and 52, Wang *et al.*, teach that the target nucleic acid is amplified using polymerase chain reaction (see column 2, lines 32-39).

Wang *et al.*, do not teach that detection of an increase in the signal indicates the presence of the target nucleic acid in the sample as recited in claim 47. However, Wang *et al.*, teach monitoring fluorescent emission change of said acceptor fluorophore (ie., decrease of the acceptor fluorophore) upon irradiation of said donor fluorophore with an excitation light, said change being a function of the extent of said first primer being dissociated from said oligonucleotide and being incorporated into said amplification product of the target nucleic acid (see claims 1 and 3 in columns 19 and 20).

Harris teaches that an increase in donor fluorescence intensity or a decrease in acceptor fluorescence intensity is detected and/or monitored as an indication that target amplification is occurring or has occurred (see column 8, first paragraph and column 9, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 47 wherein detection of an increase in the signal (ie., an increase in donor fluorescence) indicates the presence of the target nucleic acid in the sample in view of the patents of Wang *et al.*, and Harris. One having ordinary skill in the art would have been motivated to do so because Harris suggests that an increase in donor fluorescence intensity or a decrease in acceptor fluorescence intensity is used as an indication that target amplification is occurring or has occurred (see

~~column 8, first paragraph and column 9, second paragraph) and the simple replacement of one~~ well known detection method (i.e., the method for detecting a decrease in acceptor fluorescence intensity taught by Wang *et al.*,) from another well known detection method (i.e., the method for detecting an increase in donor fluorescence intensity taught by Harris,) during the process of detecting the target nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the detection method taught by Wang *et al..*, and the method taught by Harris are used for the same purpose (ie., used as an indication that target amplification is occurring or has occurred or presence of target sequence) and are exchangeable (see column 8, first paragraph and column 9, second paragraph).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

7. Claims 40-42, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, (US Patent No. 5,942,391, published on August 24, 1999) in view of Wang *et al.*, and Harris.

Regarding claims 40, 41, 45, and 46, since, in a method for detecting a target nucleic acid in a sample, Zhang *et al.*, teach: (a) contacting said nucleic acid in said sample in a reaction vessel under conditions that allow nucleic acid hybridization between complementary sequences in nucleic acids with oligonucleotide probes in the presence of paramagnetic particles coated

with a ligand binding moiety, said oligonucleotide probes comprising one or more capture/amplification probes, each having a 3' nucleotide sequence that is neither complementary nor hybridizable to a nucleotide sequence in the target nucleic acid, and a 5' nucleotide sequence that is complementary and hybridizable to a nucleotide sequence in the target nucleic acid, or a 5' nucleotide sequence that is neither complementary nor hybridizable to a nucleotide sequence in the target nucleic acid, and a 3' nucleotide sequence that is complementary and hybridizable to a nucleotide sequence in the target nucleic acid, each capture/amplification probe further having a ligand bound to the non-complementary sequence of the probe, wherein said ligand is capable of binding to and forming an affinity pair with said ligand binding moiety coated onto said paramagnetic particles; said oligonucleotide probes further comprising a circularizable amplification probe having 3' and 5' regions that are complementary to adjacent but noncontiguous sequences in the target nucleic acid, said 3' and 5' regions separated by a linker region that is neither complementary nor hybridizable to a nucleotide sequence in the target nucleic acid, such that a complex is formed comprising the target nucleic acid, circularizable probe, capture/amplification probes and paramagnetic particles, wherein the capture/amplification probes are hybridized to the complementary nucleotide sequences in the target nucleic acid and are bound to the paramagnetic particles through the binding of the ligand on the capture/amplification probe to the ligand binding moiety on the paramagnetic particles, and the circularizable probe is bound on its 3' and 5' ends to adjacent but noncontiguous sequences in the target nucleic acid; and (c) ligating the 3' and 5' ends of said circularizable probe with a ligating agent that joins nucleotide sequences such that a circular amplification probe is formed (see claim 1 in columns 67-69 and Figure 1), Zhang *et al.*, disclose that the

~~circular oligonucleotide probe is formed by ligating the 3' and 5' ends of a linear oligonucleotide~~ probe (ie., an oligonucleotide probe taught by Zhang *et al.*,) comprising 3' and 5' regions complementary to adjacent sequences in the target nucleic acid under conditions that allow hybridization between complementary sequences in the target nucleic acid and the linear oligonucleotide probe as recited in claim 41. Since, since Zhang *et al.*, teach that, after the circular oligonucleotide probe is formed, the circular oligonucleotide probe contacts with the target nucleic acid, Zhang *et al.*, disclose contacting the nucleic acid with a circular oligonucleotide probe under conditions that allow hybridization between complementary sequences in the target nucleic acid and the circular oligonucleotide probe as recited in (a) of claim 40. Since, in a method for detecting a target nucleic acid in a sample, Zhang *et al.*, further teach: (d) amplifying said circular amplification probe by contacting said complex with a first extension primer that is complementary and hybridizable to a portion of the linker region of the circular amplification probe and a second extension primer that is substantially identical to a portion of the linker region of the circular amplification probe that does not overlap with the portion of the linker region to which the first extension primer is complementary, dNTPs, and a DNA polymerase having strand displacement activity, under conditions whereby the first extension primer is extended around the circle for multiple revolutions to form a single stranded DNA of repeating units complementary to the sequence of the circular probe, and multiple copies of the second extension primer hybridize to complementary regions of the single stranded DNA and are extended by the DNA polymerase to provide extension products, and whereby the extension products of the second extension primers displace downstream copies of the second extension primers and corresponding extension products of said downstream copies to provide

displaced single strands to which multiple copies of said first extension primer bind and are extended by the DNA polymerase; (e) allowing said amplification to proceed until multiple copies of double stranded amplified DNA of varying lengths are produced; and (f) detecting said amplified DNA, wherein detection thereof indicates the presence of the target nucleic acid in the clinical sample, Zhang *et al.*, disclose adding a first primer wherein the first primer comprises (A) a first sequence that is complementary to the circular probe as recited in b) of claim 40, adding a DNA polymerase as recited in c) of claim 40, and detection indicates the presence of the target nucleic acid in the sample as recited in d) of claim 40, the circular probe is amplified using an amplification method selected from the group consisting of polymerase chain reaction, strand displacement amplification, transcription mediated amplification, RAM and primer extension wherein the amplification method is RAM as recited in claims 45 and 46.

Zhang *et al.*, do not disclose adding a primer pair comprising a first primer and a second primer wherein (i) the first primer of the pair comprises (A) a first sequence that is complementary to the circular probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a signal generating moiety; (ii) the second primer of the pair comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited as recited in (b) of claim 40, and detecting an increase in the signal which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety as recited in (d) of claim 40, and disclose that the signal generating moiety is a fluorescent agent as recited in claim 42.

The teachings of Wang *et al.*, have been summarized previously, *supra*. Wang *et al.*, teach adding a primer pair comprising a first primer and a second primer wherein (i) the first primer of the pair comprises (A) a first sequence that is complementary to the circular probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a signal generating moiety; (ii) the second primer (ie., the oligonucleotide which is incapable of acting as a primer for said polymerase of the pair taught by Wang *et al.*,) comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited as recited in (b) of claim 40 and also teach that the signal generating moiety is a fluorescent agent as recited in claim 42 (see column 3, second paragraph, columns 19 and 20, claims 1 and 3, and Figure 1).

Since Harris teaches that an increase in donor fluorescence intensity or a decrease in acceptor fluorescence intensity is detected and/or monitored as an indication that target amplification is occurring or has occurred (see column 8, first paragraph and column 9, second paragraph), Harris discloses detecting an increase in the signal (ie., an increase in donor fluorescence intensity) which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety as recited in (d) of claim 40.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 40 wherein (i) the first primer of the pair comprises (A) a first sequence that is complementary to the circular probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a

signal generating moiety; (ii) the second primer comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited, and wherein an increase in the signal which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety is detected in view of the patents of Zhang *et al.*, Wang *et al.*, and Harris. One having ordinary skill in the art would have been motivated to do so because Wang *et al.*, have successfully detected the target nucleic acid in the sample by detecting a change in the signal which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety and the simple replacement of one well known detection method (i.e., the method taught by Zhang *et al.*,) from another well known detection method (i.e., the method taught by Wang *et al.*,) during the process of detecting the target nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the detection method taught by Wang *et al..*, would eliminate or reduce nonspecific priming events (see column 7, second paragraph) and the detection method for detecting a decrease in acceptor fluorescence intensity taught by Wang *et al..*, and the method for detecting an increase in donor fluorescence intensity taught by Harris are used for the same purpose (ie., used as an indication that target amplification is occurring or has occurred or presence of target sequence) and are exchangeable (see column 8, first paragraph and column 9, second paragraph).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

8. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, in view of Wang *et al.*, and Harris as applied to claims 40-42, 45, and 46 above, and further in view of Heller (US Patent No. 5,532, 129, published on July 2, 1996).

The teachings of Zhang *et al.*, Wang *et al.*, and Harris have been summarized previously, *supra.*

Zhang *et al.*, Wang *et al.*, and Harris do not disclose that the signal generating moiety (ie., donor) is a chemiluminescent agent as recited in claim 43.

Heller teaches that either a fluorphore or a chemiluminescent group is used as a donor for non-radiative energy transfer (see column 3, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 43 wherein the signal generating moiety is a chemiluminescent agent in view of the patents of Zhang *et al.*, Wang *et al.*, Harris, and Heller. One having ordinary skill in the art would have been motivated to do so because Heller has successfully used a fluorphore or a chemiluminescent group as a donor for non-radiative energy transfer, and the simple replacement of one kind of signal generating moiety (i.e., a fluorescent donor taught by Wang *et al.*,) from another kind of signal generating moiety (i.e., chemiluminescent donor taught Heller) during the process of performing

the method recited in claim 43 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because either a fluorphore or a chemiluminescent group is used as a donor for energy transfer and they are exchangeable (see Heller, column 3, second paragraph).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

9. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, in view of Wang *et al.*, Harris, and Heller as applied to claims 40-43, 45, and 46 above, and further in view of Segev (US Patent No. 5, 437, 977, published on August 1, 1995).

The teachings of Zhang *et al.*, Wang *et al.*, Harris, and Heller have been summarized previously, *supra.*

Zhang *et al.*, Wang *et al.*, Harris, and Heller do not disclose that the signal generating moiety is an enzyme or enzyme substrate as recited in claim 44.

Segev teaches that non-radiative energy transfer is finished by a suitable chemiluminescent catalyst such as peroxidase and luciferase and a suitable absorber/emitter (see column 7, last paragraph and column 8, first paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 44 wherein the signal generating moiety is an enzyme in view of the patents of Zhang *et al.*, Wang *et al.*, Harris, Heller and Segev. One having ordinary skill in the art would have been motivated to do so because Segev has successfully used a suitable chemiluminescent catalyst such as peroxidase or luciferase and a suitable absorber/emitter for non-radiative energy transfer, and the simple replacement of one kind of chemiluminescent agent related non-radiative energy transfer method (i.e., the method taught by Heller) from another kind of chemiluminescent agent related non-radiative energy transfer method (i.e., the method taught by Segev) during the process of performing the method recited in claim 44 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Heller and the method taught by Segev are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

10. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang *et al.*, in view of Harris as applied to claims 47, 48, 51, and 52 above, and further in view of Heller (1996).

The teachings of Wang *et al.*, and Harris have been summarized previously, *supra.*

Wang *et al.*, and Harris do not disclose that the signal generating moiety (ie., donor) is a chemiluminescent agent as recited in claim 49.

Heller teaches that either a fluorphore or a chemiluminescent group is used as a donor for non-radiative energy transfer (see column 3, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 43 wherein the signal generating moiety is a chemiluminescent agent in view of the patents of Wang *et al.*, Harris, and Heller. One having ordinary skill in the art would have been motivated to do so because Heller has successfully used a fluorphore or a chemiluminescent group as a donor for non-radiative energy transfer, and the simple replacement of one kind of signal generating moiety (i.e., a fluorescent donor taught by Wang *et al.*,) from another kind of signal generating moiety (i.e., chemiluminescent a taught Heller) during the process of performing the method recited in claim 43 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because either a fluorphore or a chemiluminescent group is used as a donor for energy transfer and they are exchangeable (see Heller, column 3, second paragraph).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

11. Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang *et al.*, Harris, and Heller as applied to claims 47, 48, 51, and 52 above, and further in view of Segev (1995).

The teachings of Wang *et al.*, Harris, and Heller have been summarized previously, *supra*.

Wang *et al.*, Harris, and Heller do not disclose that the signal generating moiety is a an enzyme or enzyme substrate as recited in claim 50.

Segev teaches that non-radiative energy transfer is finished by a suitable chemiluminescent catalyst such as peroxidase and luciferase and a suitable absorber/emitter (see column 7, last paragraph and column 8, first paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 44 wherein the signal generating moiety is an enzyme in view of the patents of Wang *et al.*, Harris, Heller and Segev. One having ordinary skill in the art would have been motivated to do so because Segev has successfully used a suitable chemiluminescent catalyst such as peroxidase or luciferase and a suitable absorber/emitter for non-radiative energy transfer, and the simple replacement of one kind of chemiluminescent agent related non-radiative energy transfer method (i.e., the method taught by Heller) from another kind of chemiluminescent agent related non-radiative energy

transfer method (i.e., the method taught by Segev) during the process of performing the method recited in claim 44 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Heller and the method taught by Segev are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

In page 2, third paragraph bridging to page 3, third paragraph of applicant's remarks, applicant argues that Wang *et al.*, do not teach 'when first primer and the second primer are bound to one another, the signal is inhibited".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. Since Wang *et al.*, teach that a first fluorophore is covalently attached to said first primer and a second fluorophore is covalently attached to said oligonucleotide, with one of said first and second fluorophores being a donor fluorophore and the other being an acceptor fluorophore, so that when said first primer and said oligonucleotide are hybridized, said donor fluorophore and said acceptor fluorophore are in close proximity to allow resonance energy transfer therebetween (see claims 1 and 3 in columns 19 and 20), Wang *et al.*, teach that, when first primer (ie., said first primer having a first fluorophore or a donor fluorophore) and the

second primer (ie., said oligonucleotide having a second fluorophore or an acceptor fluorophore) are bound to one another and the signal (ie., the donor fluorophore) is inhibited.

Conclusion

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

July 24, 2006

FRANK LU
PRIMARY EXAMINER

Interview Summary	Application No.	Applicant(s)	
	09/978,261	ZHANG, DAVID Y.	
	Examiner	Art Unit	
	Frank W. Lu	1634	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Frank W. Lu*.

(2) *Ram Shukla (SPE)*.

(3) *Amy Wilson (Reg. No. 54,704)*.

(4) *Ian G. DiBgmardo (Reg No. 40,991)*.

Date of Interview: *05 April 2006*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☒ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *Claims 40-47*.

Identification of prior art discussed: *Wang et al., (US Patent No. 5,567,583)*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicants and the examiners discussed the invention to be directed to signal increase which Wang et al., do not teach. The examiner will reconsider the rejections.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

FRANK LU
PRIMARY EXAMINER

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Notice of References Cited

Application/Control No.	Applicant(s)/Patent Under Reexamination	
09/978,261	ZHANG, DAVID Y.	
Examiner	Art Unit	Page 1 of 1
Frank W. Lu	1634	

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,837,469	11-1998	Harris, James M.	435/6
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

WILSON DECLARATION

EXHIBIT B

251305.0028
(SPB:MCD)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	**David Y. Zhang**			
Application No.	:	**09/978,261**	Art Unit No.	:	**1645**
Filed	:	**October 15, 2001**	Examiner	:	**Not Yet Assigned**
For	:	**NUCLEIC ACID AMPLIFICATION METHODS**			

Date: November 6, 2002

Commissioner for Patents
Washington, DC 20231

TRANSMITTAL OF SUPPLEMENTAL DECLARATION AND POWER OF ATTORNEY

Sir:

Enclosed herewith is a Supplemental Declaration and Power of Attorney for the captioned application.

No fee is deemed necessary in connection with the filing of this Supplemental Declaration and Power of Attorney. However, if any fee is due the amount of such fee may be charged to Deposit Account No. 19-4709.

Certificate of Mailing (37 C.F.R. 1.8)
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner for Patents, Washington, D.C. 20231, on November 6, 2002.

Typed or printed name of person signing this certificate:

Jennifer Bartolo

Signature: Jennifer Bartolo

Respectfully submitted,

for Mary C. D'Arrigo, Reg. No. 37,306

Steven B. Pokotilow
Registration No. 26,405
Attorney for Applicant
STROOCK & STROOCK & LAVAN, LLP
180 Maiden Lane
New York, New York 10038-4982
(212)806-5400

COMBINED DECLARATIONAND POWER OF ATTORNEY FOR PATENT APPLICATION
(Page 1)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

the specification of which

☐ is attached hereto

☒ was filed on **October 15, 2001** as United States Patent Application No. or PCT International Application No. **09/978,261** and was amended on **October 22, 2002** (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b), of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designates at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

Country	Application No	Filed (Day/Mo./Yr.)	Priority Claimed (Yes unless box is checked)
			☐
			☐
			☐
			☐
			☐

COMBINED DECLARATIONAND POWER OF ATTORNEY FOR PATENT APPLICATION
(Page 2)

I hereby claim the benefit under Title 35. United States Code, Section 119(e) of any United States provisional application(s) listed below

Application No	Filed (Day/Mo./Yr.)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Application No.	Filed (Day/Mo./Yr.)	Status (Patented, Pending, Abandoned)
08/263,937	**June 22, 1994**	**Abandoned**
PCT/US95/07671	**June 14, 1995**	
08/596,331	**May 20, 1996**	**Abandoned**
		See Second page 2

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (list name and registration numbers).

Lawrence Rosenthal, Reg. No. 24,377
Steven B. Pokotilow, Reg. No. 26,405
James J. DeCarlo, Reg. No. 36,120
Matthew W. Siegal, Reg. No. 32,941
David L. Schaeffer, Reg. No. 32,716

COMBINED DECLARATIONAND POWER OF ATTORNEY
FOR PATENT APPLICATION
(Page 2)

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below

Application No	Filed (Day/Mo./Yr.)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Application No.	Filed (Day/Mo./Yr.)	Status (Patented, Pending, Abandoned)
08/690,494	**July 31, 1996**	**Patented**
08/909,031	**August 11, 1997**	**Abandoned**
09/299,217	**April 23, 1999**	**Pending**
09/728,265	**December 1, 2000**	**Pending**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (list name and registration numbers).

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Matthew W. Siegal, Reg. No. 32,941
David L. Schaeffer, Reg. No. 32,716

COMBINED DECLARATIONAND POWER OF ATTORNEY
FOR PATENT APPLICATION
(Page 3)

Send Correspondence to:

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Direct Telephone Calls to: (name and telephone number)

(212) 806-5400

Full Name of Sole or First Inventor: **David Y. Zhang**

Inventor's signature: _____ Date: 11/5/02

Citizen/Subject of: **United States of America**

Residence: **80-73 Chevy Chase Street**

Jamaica, New York 11432 USA

Post Office Address: **Jamaica, New York**

Full Name of Second Inventor, if any: _____

Inventor's signature: _____ Date: _____

Citizen/Subject of: _____

Residence: _____

_____

Post Office Address: _____

_____